AD_____

Award Number: DAMD17-02-1-0569

TITLE: Evaluation of DNA Methylation as a Target for Intraductal Therapy for Ductal Carcinoma in situ of the Breast

PRINCIPAL INVESTIGATOR: Kristin A. Skinner, M.D.

CONTRACTING ORGANIZATION: New York University School of Medicine
New York, New York 10016

REPORT DATE: August 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 2004	Annual (15 Jul 03 - 15 Jul 04)

4. TITLE AND SUBTITLE
Evaluation of DNA Methylation as a Target for Intraductal Therapy for Ductal Carcinoma in situ of the Breast

5. FUNDING NUMBERS
DAMD17-02-1-0569

6. AUTHOR(S)
Kristin A. Skinner, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
New York University School of Medicine
New York, New York 10016

E-Mail: kristin.skinner@med.nyu.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

Ductal carcinoma *in situ*(DCIS), the preinvasive form of infiltrating ductal breast cancer, accounts for 20-30% of breast cancers and is treated surgically. In DCIS, the malignant cells are confined within the basement membrane. DCIS is a local disease, and so an ideal candidate for local therapies. DNA methylation is one mechanism for tumor suppressor gene inactivation. It is an early event in the course of malignant progression. Because methylation is a potentially reversible mechanism for tumor suppressor gene inactivation, it is an intriguing target for molecular therapeutics. Drugs, such as 5-aza-deoxycytidine (DAC), are available that can reverse methylation changes and prevent neoplasia *in vivo*. **Hypothesis: DNA Methylation is altered in DCIS and is a therapeutic target for intraductal therapy. Specific Aim 1:** Document the methylation status of tumor suppressor genes in DCIS. **Specific Aim 2:** Document the feasibility of an intraductal approach to DCIS. **Specific Aim 3:** Identify the dose(s) of DAC with biologic activity and acceptable side effects when delivered intraductally to patients with DCIS (Phase I trial). The ultimate goal of this proposal is to evaluate DNA methylation as a target for intraductal therapy. The results of this study could revolutionize the way we treat DCIS.

14. SUBJECT TERMS
Ductal Carcinoma in situ of the Breast, intraductal therapy, ductal Lavage, DNA methylation, 5-aza-2'-deoxycytidine, decitidine

15. NUMBER OF PAGES
5

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Introduction: Ductal carcinoma *in situ*(DCIS), the preinvasive form of infiltrating ductal carcinoma of the breast, currently accounts for 20-30% of breast cancers and is treated by surgically removing the involved ducts. In DCIS, the malignant cells have not having invaded through the basement membrane and therefore have not gained access to the lymphatics or the systemic circulation. DCIS is a local disease, and so an ideal candidate for local therapies. DNA methylation is one mechanism for tumor suppressor gene inactivation. It is an early event in the course of malignant progression in several tumor systems. Because methylation is a potentially reversible mechanism for tumor suppressor gene inactivation, it is an intriguing target for molecular therapeutics. Drugs, such as 5-aza-deoxycytidine (DAC), are available that can reverse methylation changes and prevent tumor suppressor gene-related neoplasia *in vivo*. **Hypothesis: DNA Methylation is altered in DCIS and is a therapeutic target for intraductal therapy. Specific Aim 1:** To document the methylation status of a panel of tumor suppressor genes in DCIS. **Specific Aim 2:** Document the feasibility of an intraductal approach to DCIS. **Specific Aim 3:** Identify a dose or range of doses of DAC with biologic activity and acceptable side effects when delivered intraductally to patients with DCIS (Phase I trial). The ultimate goal of this proposal is to evaluate DNA methylation as a target for intraductal therapy. The results of this study could revolutionize the way we treat DCIS.

Body: Unfortunately due to significant administrative delays, no work has yet been done on this project. As I changed institutions in 01/03, a request for transfer of the grant was made. The transfer process was initiated at the University of Southern California in 11/02. I left that institution on 12/31/02 and started at NYU in 01/03. The transfer was completed in 5/04 and the proposal is now in the final stages of IRB approval at NYU. Once the IRB has approved the protocol, it will be forwarded to your HSRRB for final approval. As a result of the significant delays in the transfer process, I have not been able to start the project. I am hopeful that final approval will be achieved in the next month or two and work can begin. Because of the delays, I am requesting a 2-year no cost extension in order to successfully complete the work.

Key Research Accomplishments:

-Response to Memorandum of Record Complete 8/12/02.

-No further action by Margaret Abramowitz, RN, Human Subjects Protection Specialist, AMDEX Corp.

-12/02 Notified by Andrea Kline of Change in Human Subjects Protection Specialist from AMDEX. Told that previous specialist had never forwarded my file to the Board for review. Acknowledged that my file was complete. Ms. Kline notified of my planned move and agreed to wait until transfer granted to submit to board.

-11/15/02 Began process of transferring grant as PI moving to NYU as of 1/1/03

-5/03 Grant transfer accomplished

-5/03 Protocol submitted to the NYU Cancer Institute to begin the IRB approval process.

-6/03 Protocol approved by the NYU Cancer Institute's Protocol Review And Management Committee and forwarded to the IRB. To be reviewed at the August IRB meeting.

-7/28/04 discussed status with Dr Beitins, the new Human Subjects Protection Specialist assigned to my grant and everything is in order at the DOD end for HSRRB submission, awaiting final NYU IRB approval.

Reportable Outcomes: None

Conclusions: No work accomplished due to administrative delays. Request 2-year no-cost extension in order to complete the project.

References: N/A

Appendices: N/A